PATENT SPECIFICATION (11) 1246606

NO DRAWINGS

(21) Application No. 18362/70 (22) Filed 17 April 1970

(31) Convention Application No. 133242 (32) Filed 28 April 1969 in

(33) Poland (PO)

(45) Complete Specification published 15 Sept. 1971

(51) International Classification C 07 d 41/08//A 61 k 27/00

(52) Index at acceptance

C2C 177—189—283 1E1K4 1E1K7 213 247 250 251 25Y 30Y 342 34Y 574 579 62X 790 KF

1246606

(54) DIBENZO-AZEPINE DERIVATIVES

(71) We, STAROGARDZKIE ZAKLADY FARMACEUTYCZNE "POLFA", a Body Corporate organised and existing under the laws of Poland, of Przedsiebiorstwo Panstwowe, Starogard-Gdanski, Pelplinska 19, Poland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be

bonyl - iminodibenzyl and treating the 5 - chlorocarbonyl - iminodibenzyl with a brominating agent to yield the 5 - chlorocarbonyl - 10 - bromoiminodibenzyl.

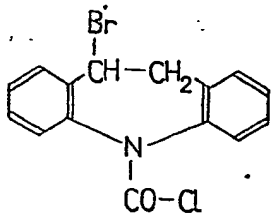
The process uses as starting material 10,11 - dihydro - 5H - dibenzo(*b*,*f*)azepine which is

ERRATUM

SPECIFICATION No. 1,246,606

Page 2, line 68, *for* "70 ml" *read* "700 ml"

THE PATENT OFFICE
30th November 1971



Formula II

which is useful as an intermediate for preparing compound (I).

This compound II may be prepared according to a process comprising reacting iminodibenzyl with phosgene to give 5 - chlorocarbonyl - iminodibenzyl and treating the 5 - chlorocarbonyl - iminodibenzyl with a brominating agent to yield the 5 - chlorocarbonyl - 10 - bromoiminodibenzyl.

The process uses as starting material 10,11 - dihydro - 5H - dibenzo(*b*,*f*)azepine which is commercially available. After crystallization from carbon tetrachloride, the said compound has a melting point of from 128 to 129° C and its composition has been confirmed by elementary analysis.

The compound II so obtained can be used to prepare compound I by dehydrobromination and amidation.

The chlorine of the chlorocarbonyl group of the compound (II) is of relatively low reactivity so that the dehydrobromination reaction can be performed without affecting the chlorine atom. Preferably the dehydrobromination and the amidation treatment are effected simultaneously by treatment with ammonia.

The dehydrobromination reaction of 5 - chlorocarbonyl - 10 - bromo - iminodibenzyl in positions 10 and 11 and simultaneously the substitution of chlorine by an amino group

SEE ERRATA SLIP ATTACHED

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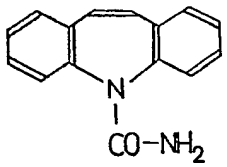
(54) DIBENZO-AZEPINE DERIVATIVES

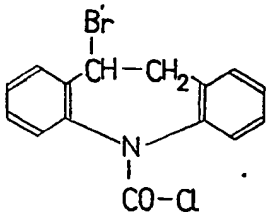
(71) We, STAROGARDZKIE ZAKLADY FARMACEUTYCZNE "POLFA", a Body Corporate organised and existing under the laws of Poland, of Przedsiebiorstwo Panstwowe, Starogard-Gdanski, Pelplinska 19, Poland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a new process for producing 5 - carbamyl - 5H - dibenzo(*b,f*)-azepine, an antiepileptic drug of the formula:



Formula I

and provides a new compound 5 - chlorocarbonyl - 10 - bromo - iminodibenzyl of the formula:

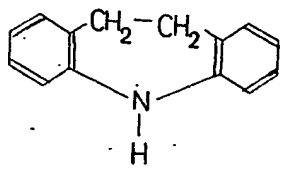


Formula II

which is useful as an intermediate for preparing compound (I).

This compound II may be prepared according to a process comprising reacting iminodibenzyl with phosgene to give 5 - chlorocarbonyl - iminodibenzyl and treating the 5 - chlorocarbonyl - iminodibenzyl with a brominating agent to yield the 5 - chlorocarbonyl - 10 - bromoiminodibenzyl.

The process uses as starting material 10,11 - dihydro - 5H - dibenzo(*b,f*)azepine which is called also iminodibenzyl and which has the structure:



Formula III

The brominating agent must be selected to brominate the 10 or 11 position of 5 - chlorocarbonyl - iminodibenzyl. Advantageously 1,3-dibromo - 5,5 - dimethylhydantoin is used as the brominating agent. The resulting 5 - chlorocarbonyl - 10 - bromoiminodibenzyl can be isolated in crystalline form by conventional methods. After crystallization from carbon tetrachloride, the said compound has a melting point of from 128 to 129° C and its composition has been confirmed by elementary analysis.

The compound II so obtained can be used to prepare compound I by dehydrobromination and amidation.

The chlorine of the chlorocarbonyl group of the compound (II) is of relatively low reactivity so that the dehydrobromination reaction can be performed without affecting the chlorine atom. Preferably the dehydrobromination and the amidation treatment are effected simultaneously by treatment with ammonia.

The dehydrobromination reaction of 5 - chlorocarbonyl - 10 - bromo - iminodibenzyl in positions 10 and 11 and simultaneously the substitution of chlorine by an amino group

may be carried out by the action of ammonia in an aromatic hydrocarbon medium, advantageously benzene, at a temperature of from 80 to 130° C to give 5 - carbamyl - 5H - dibenzo(*b*,*f*)azepine in good yield.

Alternatively the dehydrobromination may be separately effected e.g. by heating in the presence of a polyamide such as polycaprolactam. During the dehydrobromination additionally a salt of the general formula Me_mX_n type may be present where Me denotes an alkali metal atom or alkaline earth metal atom, X is an acid radical of a weak acid and *m* and *n* are 1 or 2 and comprise salts such as sodium carbonate, potassium carbonate and calcium carbonate etc. The salts may be used in an inert organic solvent medium particularly an aromatic hydrocarbon such as toluene or xylene. The dehydrobromination product is then amidated by treatment with ammonia.

The invention is illustrated by the following Examples.

EXAMPLE I

19.5 g of iminodibenzyl are dissolved in 100 ml of toluene and the solution is saturated with phosgene at the boiling temperature. After the evolution of hydrogen chloride has stopped, the solution is concentrated to about 1/5 of the original volume and, after cooling, the precipitated 5 - chlorocarbonyl - iminodibenzyl is filtered off. The yield is 24.5 g i.e. 95%. The melting point is from 120 to 121° C.

25.8 g of 5 - chlorocarbonyl - iminodibenzyl are dissolved in 400 ml of carbon tetrachloride and 14.6 g of 1,3 - dibromo - 5,5 - dimethylhydantoin and 0.2 g of benzoyl peroxide acting as a catalyst are added. The mixture is heated at the boiling temperature until bromine has disappeared from the solution. After the reaction mixture has been cooled, dimethylhydantoin is filtered off, the solution is washed with water, concentrated to about 60 ml at a temperature less than 60° C and, after cooling, 5 - chlorocarbonyl - 10 - bromoiminodibenzyl is filtered off. The yield is 30 g i.e. 90%. After recrystallization the melting point of the product is from 128 to 129° C.

33.7 g of 5 - chlorocarbonyl - 10 - bromo-iminodibenzyl in 500 ml of benzene are heated in an autoclave at a temperature of about 100° C with gaseous ammonia for approximately 3 hours. After the reaction mixture has been cooled, the separated inorganic salts are filtered off and the filtrate is concentrated to about 70 ml. After cooling, the crystallized product is filtered off and then washed with dilute hydrochloric acid and then with water. After recrystallization from a water-methanol solution, pure 5 - carbamyl - 5H - dibenzo-(*b*,*f*)azepine with a melting point of from 190 to 191° C is obtained.

EXAMPLE II

33.7 g of 5 - chlorocarbonyl - 10 - bromo-iminodibenzyl obtained as in Example I, are dissolved in 70 ml of xylene and 66 g. of polycaprolactam and 35 g of anhydrous potassium carbonate are added. The mixture is heated at the boiling temperature for approximately 8 hours. After the reaction mixture has been cooled, the precipitate is filtered off and the filtrate is subjected to the action of gaseous ammonia at a temperature of approximately 90° C. After cooling, the crystallized product is filtered off, the ammonium chloride is washed away with water and the product is re-crystallized from a water-methanol solution. The yield of pure 5 - carbamyl - 5H - dibenzo(*b*,*f*)azepine is 22.4 g i.e. 85%. The melting point is from 190 to 191° C.

EXAMPLE III

33.7 g of 5 - chlorocarbonyl - 10 - bromo-iminodibenzyl are dissolved in 700 ml of xylene and 60 g of polycaprolactam and 28 g of anhydrous sodium carbonate are added. The mixture is heated at the boiling temperature for approximately 7 hours. After cooling, the precipitate is filtered off and the filtrate is concentrated under reduced pressure to a volume of 100 ml. After further cooling, the crystallized product is filtered off and dried.

The product, 5 - chlorocarbonyl - 5H - dibenz(*b*,*f*)azepine, is dissolved in 200 ml of a 3 N methanolic ammonia solution and heated in an autoclave at a temperature of from 80 to 90° C for 3 hours. After cooling, the crystallized 5 - carbamyl - 5H - dibenzo(*b*,*f*)azepine is filtered off and washed with water. The total yield is 19.5 g i.e. 83%.

WHAT WE CLAIM IS:—

1. 5 - Chlorocarbonyl - 10 - bromo -iminodibenzyl.
2. A process for producing the compound of claim 1 comprising reacting iminodibenzyl with phosgene to give 5 - chlorocarbonyl - iminodibenzyl and treating the 5-chlorocarbonyl - iminodibenzyl with a brominating agent to yield the 5 - chlorocarbonyl - 10 - bromo - iminodibenzyl.
3. A process according to claim 2 in which the brominating agent is 1,3 - dibromo - 5,5 - dimethyl - hydantoin.
4. A process for the preparation of 5 - chlorocarbonyl - 10 - bromo - iminodibenzyl substantially as described in Example 1.
5. 5 - Chlorocarbonyl - 10 - bromo - iminodibenzyl when prepared by a process according to any of claims 2 to 4.
6. A process of preparing 5 - carbamyl - 5H - dibenzo(*b*,*f*)azepine comprising subjecting the compound of claim 1 or 5 to dehydrobromination and amidation.
7. A process according to claim 6 in which the dehydrobromination and amidation are

effected simultaneously by treatment with ammonia.

8. A process according to claim 6 in which the dehydrobromination is effected in the presence of a polyamide to give 5 - chlorocarbonyl - 5H - dibenz(*b*,*f*)azepine which is then amidated by treatment with ammonia.

9. A process according to any of claims 6 or 8 in which the dehydrobromination is effected in the presence of a polycaprolactam to give 5 - chlorocarbonyl - 5H - dibenz(*b*,*f*)-azepine which is then amidated by treatment with ammonia.

10. A process according to either of claims 8 and 9 in which the dehydrobromination is effected in the presence of a salt of the general formula Me_mX_n, where Me is an alkali metal or alkaline earth metal and X is an acid radical of a weak acid and *m* and *n* are 1 or 2.

11. A process acording to claim 10 in which the salt is sodium carbonate.

12. A process for the preparation of 5-carbamyl - 5H - dibenzo(*b*,*f*)azepine substantially as described in any of the Examples.

13. 5 - Carbamyl - 5H - dibenzo(*b*,*f*)azepine when prepared from 5 - chlorocarbonyl - 10 - bromo - iminodibenzyl.

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